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Case Report
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The Diagnosis Challenge of Cutaneous Localization of Hepatosplenic T-Cell Lymphoma

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Abstract

Hepatosplenic T-cell Lymphoma (HSTL) is characterized by predominant involvement of liver, spleen and bone marrow, and an often aggressive course. Lymphadenopathy is rarely observed and involvement of skin is exceptional making recognition of cutaneous localization a diagnostic challenge. We report a case of 30-year-old woman presented with generalized pruritic and erythematous plaques, irregular fever, and obvious abdominal distension. The patient was treated for psoriasis for the past 7 years, by various doctors in tertiary centers, with topical steroid and methotrexate without much control. The patient's condition further worsened, and she developed multiple new plaques in the past 8 months. Investigations revealed thrombocytopenia with hepatosplenomegaly. Skin biopsy showed atypical lymphoid cells involving the dermis with expression of CD3, CD7, CD56 and cytotoxic granule-associated proteins (TIA1, Granzyme B and Perforin), and were negative for CD20, CD2, CD4, CD5, CD8, CD30, ALK and TdT (Terminal deoxynucleotidyl Transferase). The diagnosis of a skin localization of a HSTL was performed. The patient was treated with chemotherapy.

Keywords: Hepatosplenic T-cell lymphoma; Cutaneous lymphoma; Skin

Introduction

Hepatosplenic T-cell Lymphoma (HSTL) represents a rare aggressive form of peripheral T-cell lymphoma representing less than 1% of all non-Hodgkin's lymphomas and accounting for 1.4% of all peripheral T-cell and Natural Killer (NK) cell lymphomas [1]. It affects mainly adolescents and young adults, with a male predominance. Clinically, the HSTL is characterized by predominant involvement of liver, spleen, and bone marrow, unusual lymph node involvement, and an often aggressive course with a mean survival of less than 2 years [2].

Involvement of skin is exceptional, making recognition of cutaneous localization a diagnostic challenge. In the literature review, few data are available. To the best of our knowledge, this report provides the fifth detailed account of skin involvement by HSTL.

Case Presentation

A 30-year old woman presented with generalized pruritic and erythematous plaques, irregular fever, and obvious abdominal distension. The patient was treated for psoriasis for the past 7 years by various doctors in tertiary centers, with topical steroids and methotrexate without much control. The patient's condition further worsened, and she developed multiple new plaques in the past 8 months. Physical examination was significant for a hepatomegaly and ascites with generalized cutaneous pink erythematous papules. No palpable lymphadenopathy was noted. Laboratory studies revealed the following: Thrombocytopenia (70,000/mm^3) and anemia (7 g/dl). Renal function and liver function tests were within normal limits. Serum Lactate Dehydrogenase (LDH) was 600 U/L (normal level, 84 to 240 U/L) and uric acid was 9.0 mg/dL (normal level, 2.6 to 6.8 mg/dL). Computed Tomography (CT) of the chest, abdomen and pelvis revealed 6 cm × 7 cm mass lesion in left lobe of liver. There was no evidence of lymphadenopathy. Skin biopsy revealed a dermal atypical lymphocytic infiltrate around the skin appendages and vessels without epidermotropism (Figure 1). This infiltrate was constituted of clusters of monotonous small to medium-sized neoplastic cells with condensed nuclei and a rim of pale cytoplasm (Figure 2). No granulomatous changes were observed. Phenotypic examination showed that the neoplastic cells expressed CD3 (Figure 3), CD7, CD56 (Figure 4) and showed an activated cytotoxic immunophenotype (TIA1+ and granzyme B+), and were negative

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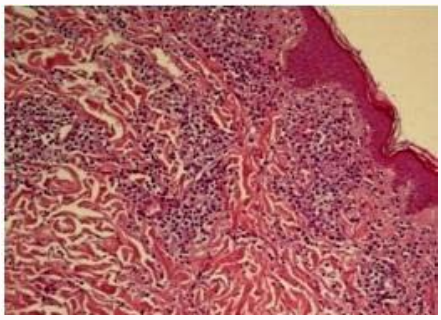

Figure 1: Dermal atypical lymphocytic infiltrate without epidermotropism.

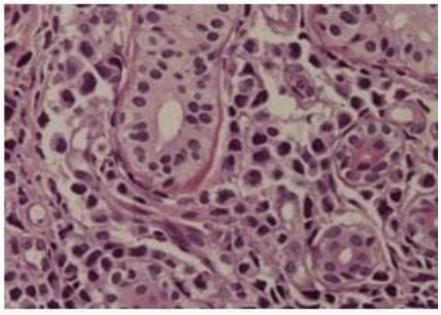

Figure 2: Atypical lymphocytic infiltrate around the skin appendages constituted of monotonous small to medium-sized neoplastic cells with condensed nuclei and a rim of pale cytoplasm.

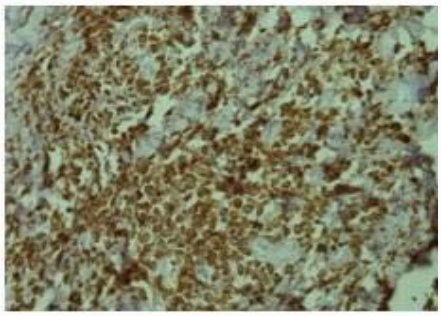

Figure 3: Positive staining with CD3.

for CD20, CD2, CD4, CD5, CD8, CD30, ALK and TdT (Terminal deoxynucleotidyl Transferase). The diagnosis of a skin localization of a HSTL was performed.

The bone marrow biopsy was massively infiltrated with the same atypical lymphoid cells with narrow cytoplasm, large and hyperchromatic nuclei. The cells were situated in the form of small islets or in an intra-sinusoidal fashion. The immunohistochemical examination revealed that the above-depicted cells gave positive reaction with CD3.

The patient was diagnosed with stage IVB hepatosplenic T-cell lymphoma and underwent CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) but died one week later. A postmortem examination was not performed.

The consent was gathered from the patient investigated in this study before her death.

Discussion

We report an exceptional case of HSTL with skin lesions at

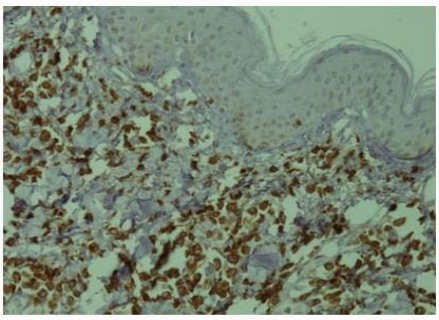

Figure 4: Positive staining with CD56.

presentation. Review of the literature disclosed description of only four HSTL case with cutaneous lesions and documentation of lymphomatous skin involvement at the time of presentation (Table 1) [1-4].

HSTL, which occurs predominantly in young male adults with a median onset age of 34 years. The common clinical presentation is hepatosplenomegaly and symptoms secondary to pancytopenia [1,5]. A number of HSTL cases have been reported in patient with inflammatory bowel disease being treated with immunosuppressive therapy [6].

Rare cases have been reported in patient with psoriasis receiving Tumor Necrosis Factor alpha (TNF-α) inhibitor therapy [7]. Our patient has been treated with corticosteroids and immunomodulators (methotrexate) for an unknown duration before the diagnosis of HSTL.

The first case is mentioned in the series of Lu et al. [1], a 12-year-old boy who presented with skin rash and abdominal distension, and who underwent splenectomy, wedge resection of the liver and skin biopsy. This latter revealed a neoplastic lymphoid infiltrate of the upper dermis accumulating around the skin, appendages, and vessels without epidermotropism. The patient received CHOP chemotherapy after splenectomy and responded well [1].

Our patient presented with skin lesions displaying generalized erythema. Microscopically, the neoplastic lymphoid cells infiltrated the dermis with no epidermal change and no epidermotropism. These cells had morphology and immunophenotypes similar to those of the tumor cells infiltrating the bone marrow. The results support the diagnosis of skin involvement by HSTL.

It is however necessary to distinguish HSTL of γδ phenotype from other types of peripheral T-cell lymphoma, which occur primarily in the skin or are secondarily disseminated to skin, especially Primary Cutaneous γδ T-cell Lymphoma (PCGDTCL). The clinicopathologic features of the 2 tumors are completely different. PCGDTCL is an uncommon form of cutaneous lymphoma often presenting with generalized patches or plaques, of skin lesions preferentially affecting the extremities, with or without epidermal necrosis and ulceration [8]. Spleen, liver, and bone marrow involvement is uncommon. PCGDTCL manifests three major patterns of involvement: Epidermotropic, dermal, and subcutaneous [8]. Epidermal infiltration may vary from mild epidermotropism to marked pagetoid reticulosis-like infiltrates. The subcutaneous cases may show rimming of fat cells, similar to subcutaneous panniculitis-like T-cell lymphoma of αβ origin, in addition to dermal and/or epidermal involvement [8]. The neoplastic cells are usually medium to large in size with

Table 1: Clinicopathologic features of five patients with cutaneous HSTL including four previously reported in the literature.

Case	Sex/ Age (years)	Medical history	Skin lesions	Presenting signs	Histologic features of skin involvement	Immunohistochemical study
Case 1 Lu et al. [1]	M/12	No known autoimmune disease or source of immunosuppression	Generalized pink cutaneous papules	Hepatosplenomegaly, anemia, hematuria, albuminuria	Small to medium cells. No epidermotropism. Dermal infiltrate, periadnexial and perivascular	CD3(+), CD20(-), and showed an activated cytotoxic immunophenotype (TIA1+ and granzyme B+)
Case 2 Guo et al. [10]	M/12	No known autoimmune disease or source of immunosuppression	hemorrhagic papules on abdomen and extremities	Lymphadenopathy, hepatosplenomegaly	Small atypical lymphoid cells. Infiltrate the upper dermis surrounding the appendages	CD3(+), CD8 (+), showed an activated cytotoxic immunophenotype (TIA1), CD4(-), CD20(-) and CD56(-)
Case3 Karpate et al. [8]	F/62	Bilateral breast cancer and diabetes; no known immunosuppression	Erythematous ill-defined circular rash over the trunk and abdomen	Hepatosplenomegaly, pancytopenia, fever	Medium to large cells. Epidermotropism. Dermal infiltrate, periadnexial and perivascular. No intravascular infiltrate	CD3(+), CD4(-), CD5, CD7(-), CD8(-), CD30 (-)CD56(-), and showed an activated cytotoxic immunophenotype (TIA1+ and granzyme B+)
Case 4 Paes et al. [9]	F/56	No known autoimmune disease or source of immunosuppression	Diffusely scattered hyperchromic skin lesions	lymphadenopathy, hepatosplenomegaly, pancytopenia	Dermal infiltration by monomorphic cells	CD3(+), CD57 (+), CD45 (-) and CD20 (-).
Case 5 Our case	F/30	Psoriasis for the past 7 years, treated with topical steroid and methotrexate	Generalized pink erythematous papules	Hepatomegaly, ascites, anemia, thrombocytopenia	Small to medium cells without epidermotropism. Dermal infiltrate, periadnexial and perivascular	CD3 (+), CD7(+), CD56 (+) and showed an activated cytotoxic immunophenotype (TIA1+ and granzyme B+), and CD20(-), CD2(-), CD4(-), CD5(-), CD8(-), CD30(-), ALK and TdT(-)

coarsely clumped chromatin. Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angio-invasion. The most characteristic phenotype is CD3+, CD2+, CD5-, CD7 ±, CD56+ CD4-, CD8 ±, with strong expression of cytotoxic proteins. Most PCGDTCL cases express the VD2 epitope [8,9]. Other cutaneous T lymphoma can be ruled out by immunohistochemistry.

In the updated World Health Organization classification of tumors of hematopoietic and lymphoid tissues, both the γδ type and the αβ type of HSTL are recognized as distinct entities of malignant lymphoma [8].

HSTL of γδ phenotype is preferentially localized within the spleen red pulp, liver and bone marrow. All patients usually present with hepatosplenomegaly and variable degrees of hematologic abnormalities, reflecting active cytokine production by the tumor. Lymphadenopathy is rare and sometimes associated with infiltration of other organs by malignant cells in the terminal stage of the disease [9]. Bone marrow involvement is found in approximatively 60% of patients at diagnosis, with preferential sinusoidal distribution of the T cells [9].

The most common phenotype of hepatosplenic γδ T cell lymphoma is CD2+ (97% of cases), CD3+ (100% of cases), CD4-, CD5-, CD7+ (65% of cases), CD8 ± (weak to strong positivity seen in 16 %), TCR γδ+ (100% of cases). Most γδ cases express the Vδ1 epitope (80% of cases). NK-related antigens CD16 and CD56 are frequently expressed in, respectively, 52% and 67%. Data regarding expressing cytotoxic granule-associated proteins are conflicting; neoplastic cells usually express TIA1 and granzyme M, but are usually negative for granzyme B and perforine. Epstein-Barr virus is generally absent.

In the literature review, skin lesions were reported in only three patients with HSTL.

The CHOP or CHOP-like regimens are usually the first-line treatment for patients with HSTCL. The prognosis is poor regardless of the therapy [2,10]. According to the review by Weidmann et al. [9], 80% of patients with HSTL had died of the tumor at the time their cases were reported, and the median survival time was 8 months. New treatment modalities are under investigation to improve the prognosis of patients with HSTCL, with more insight in the biology of the malignant γδ T-cells.

Conclusion

The HSTL is a rare variant of peripheral T-cell lymphoma exhibiting aggressive behavior with a high frequency of relapses and incomplete response to chemotherapy. Skin involvement is quiet rare. A distinction from PGDTCL is important particularly in the clinically advanced generalized cases with multi organs involvement.

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